



Changes on the Scientific Side of Pharmacy.

BY

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Changes on the Scientific Side of Pharmacy.*

By Professor W. PALMER WYNNE, D.SC., F.R.S.

When the invitation was given to me to deliver the inaugural address this afternoon, I felt it was impossible to decline it, although the only reasons for the choice which I could discover were my recent appointment to the chemistry chair, and possibly my early connection with pharmacy. While appreciating the compliment most fully, I am deeply sensible, not only of the honour but the difficulty, of following the many eminent men who have lent the lustre of their names to this ceremony in previous years.

A BRIEF RETROSPECT.

On an occasion like this, when to all intents and purposes I take up the duties of Professor in this School, it is only fitting that I should recall the names of my distinguished predecessors in the chair—Fownes, Redwood, Attfield, Dunstan, Collie. In so far as I am able to continue their work and to maintain the high standard which they created, I shall owe it less to any

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efforts of mine than to the co-operation of the Council, colleagues, and students, without which success would be impossible.

It is twenty-six years ago, almost to the day, since I made my first acquaintance with pharmacy, as an apprentice in the analytical and manufacturing department of a well-known firm of chemists and druggists. Apprenticeship in analytical chemistry is not of common occurrence, and mine arose from the fact that there was no vacancy in the pharmacy, to which I should naturally have gone. Later on, when a transference was possible, other things intervened, and thus the object of my ambition—a Jacob Bell scholarship—was never attained. Although many years have elapsed since that apprenticeship came to an end, I have never ceased to be grateful for the training and experience gained during that time under the stimulating influence of my friend, Mr. H. W. Jones.

In choosing a subject for this afternoon's address, it is, perhaps, natural to turn to the changes that have taken place on what may be called the scientific side of pharmacy during recent years, and in particular to those in which progress in chemistry has played a part. The survey necessarily can only be a partial one, and deal with points in which one's interest has never waned.

THE STANDARDISATION OF GALENICALS.

The Pharmacopœia itself enables such a comparison to be made, and leaving out of account improvements in the manufacture of galenicals, which I am not competent to discuss—two points seem to me to be of especial interest. The first is the introduction of methods for standardising certain extracts and tinctures, and the second is the recognition extended to various synthetic remedies. How marked is the change may be seen from the fact that in the 1867 Pharmacopœia, under which I worked, standards were prescribed for very few drugs—I can only recall those for opium, cinchona and sweet spirit of nitre—and in this edition chloral hydrate does not find a place, its inclusion being deferred until the issue of the "Additions," in 1874. Standardisation of extracts makes its first appearance in 1885, and salicylic acid is admitted in the same year; but well-established synthetic

products, like antifebrin, antipyrine, and phenacetin are excluded until the "Additions" of 1890, salol being added in 1898.

The necessity for standardisation—probably recognised from very early times—was making itself felt in the later seventies, and many were the analyses, not only of samples of opium and bark, but also of ipecacuanha and of preparations from them which came to the laboratory for analysis. Moreover, attempts were constantly being made—with ergot, for example—to secure a greater degree of uniformity, and I well remember one interesting case that seemed to mark a distinct advance in pharmacy. Preparations of ipecacuanha being at that time quite untrustworthy, we isolated the active principles from the root and a solution of these of known alkaloidal strength was introduced as a substitute for the wine under the name liquor emetinæ. In the light of later knowledge the name can hardly be regarded as altogether happy, for doubtless the solution contained a mixture of the various alkaloids of ipecacuanha, varying in relative proportion with different samples of the root. Looking back, with the knowledge gained from Paul and Cownley's systematic investigation of the ipecacuanha alkaloids, it seems as if an opportunity was lost of carrying out much interesting work on these puzzling and, at that time, little-known substances. Such work, however, would have been possible only in a department devoted entirely to research, and the time was not ripe for experimental work of which the advantage was not immediately apparent. Enough has been said, however, to show that it was my good fortune to be trained in a laboratory imbued with the spirit of investigation, even though the time for research was necessarily limited.

It was with some gratification that, in the last edition of the Pharmacopœia I found a standard laid down for ipecacuanha products, although the strength is fixed by percentage of total alkaloids, and in this respect is no advance on the liquor emetinæ of twenty years ago. If with ipecacuanha, like cinchona and opium, standardisation does not go beyond the total alkaloidal content, it is difficult to resist the conclusion that greater certainty would be obtained by the use of the

pure alkaloids either singly or in mixtures of known and constant proportion

THE MODERN DEVELOPMENT OF ORGANIC CHEMISTRY.

Reference has been made to the 1867 Pharmacopœia, and to my mind much interest attaches to it, for it dates back almost to the time when the modern development of organic chemistry began. This development, carried on with ceaseless activity ever since, both on the theoretical and industrial side, had its origin primarily in the fact that means had been devised for unravelling the internal structure of the molecules of organic substances, and in particular those of benzene, pyridine, and other cyclic compounds. Given a substance of known structure, it became possible to study the modification in its properties effected by the introduction into, or removal from, its molecule of atoms or groups of atoms—radicals, in other words—and, conversely, knowing the radicals present in its molecule, to predict, oftentimes with considerable accuracy, the properties of the substance. This insight into the structure of molecules has received its highest industrial development in the manufacture of the so-called aniline dyes, but it is equally the cause of the rapid rise of another industry, namely, the manufacture of synthetic remedies.

Comparatively early in last century it was ascertained that the therapeutic effects of many drugs were largely due to definite organic substances—the alkaloids—contained in them, and the isolation of these in a pure state made an exact study of their physiological reaction possible. Very soon it became evident that out of the many alkaloids separated from plants of all kinds comparatively few had any therapeutic value. The well-known cases of the alkaloids of opium and cinchona serve to illustrate the point, one, or at most two, of the many present in each being of any value as remedial agents, and recognised as such in the Pharmacopœia.

How many attempts were made to prepare these costly alkaloids by synthetical means, prior to the discovery of the constitution of benzene and pyridine, cannot be known. The success achieved in the case of other products of animal or plant activity must have supplied a strong incentive to work

of this kind, and there is on record at least one attempt to synthesise quinine, namely, by oxidising aniline—an attempt which failed for reasons that could not be assigned at the time, but were rendered clear beyond dispute from the moment the constitution of the parent substances was understood. The synthesis of alkaloids still attracts attention, but although the formation in the laboratory of at least one has been achieved, and that of several others is on the verge of completion, other problems have proved to be of more immediate interest.

THE CONNECTION BETWEEN CHEMICAL STRUCTURE AND PHYSIOLOGICAL EFFECT.

The insight gained into the structure of organic substances led to the attention of chemists and pharmacologists being directed to the question of the connection between the structure or constitution of a substance and its physiological effect. The problem has proved to be by no means easy of solution, for the living organism is not under the same degree of control, and the conditions of experiment cannot be varied with the ease and certainty possible with non-living substances in a chemical laboratory. The physiological effect of a definite chemical substance may be, and often is, very complex—differing, too, not infrequently in health and disease—and until these effects are differentiated and localised it is hopeless to attempt to correlate them with the structure of the substance under investigation. These represent some of the difficulties from the physiological side, whilst on the chemical there is the uncertainty attaching to the structure of many of the alkaloids themselves. Formulæ have been devised for a few—such as papaverine, narcotine, hydrastine, conine, and nicotine; others have had their constitution partly made out—such as atropine, aconitine, morphine, quinine, cinchonine, and pilocarpine, but comparatively little is known about many others, such as brucine and strychnine.

In spite of all these difficulties, some points of great importance have been established. In the first place, alkaloids are, almost without exception, derivatives of pyridine, quinoline, or isoquinoline, and the nitrogen atom in each of these parent sub-

stances has an important influence on the properties of the alkaloid. Not the most important influence, it may be, for otherwise alkaloids so different in their effects as strychnine, brucine, thebaine, codeine, morphine, and nicotine would exhibit a greater resemblance than is actually the case, for in them this particular nitrogen atom is present in one and the same condition. Other radicals in these alkaloids evidently exert their specific effects, and hence the differences in physiological action; yet, as Crum Brown and Fraser showed more than thirty years ago, these effects are to a large extent lost, and the six alkaloids are transformed into derivatives, which, however different in chemical composition, are practically indistinguishable in their main physiological action—one resembling that of curare—by an operation that affects this particular nitrogen atom alone, and is equivalent to the transformation of ammonia into ammonium chloride—the conversion of triad into pentad nitrogen, in other words. Crum Brown and Fraser's papers mark an epoch in investigations of this kind, for, as these authors say, the results just mentioned "show that composition alone is quite insufficient to explain physiological action, and that constitution must be taken into account in every attempt to connect the chemistry of substances with their physiological action."

How true this is has been amply proved by later investigation. M'Kendrick and Dewar showed, five years later, that similar changes in structure produce similar physiological effects in the case of the parent substances pyridine and quinoline and their derivatives; and, if we confine our attention merely to the alkaloids included in the Pharmacopœia, the same point can be demonstrated beyond a doubt. Thus, morphine and codeine differ in structure only to this extent that the former contains a particular oxygen atom associated with hydrogen, codeine contains it in association with methyl. In some respects morphine and codeine have a similar physiological effect, but the narcotic properties which differentiate the two are bound up with that particular hydrogen atom, and disappear when it is replaced by methyl or other radicals. Quinine and cinchonine, strychnine and brucine are related in much the same way. Quinine differs from cinchonine only by containing a methoxyl group substi-

tuted for a particular atom of hydrogen, and strychnine from brucine by containing two hydrogen atoms in place of two methoxyl groups; small differences in structure it may be, out of enormous importance from the physiological side. Recent research tells the same story, but time will only allow me to mention the interesting case of aconitine, and its non-poisonous derivatives benzaconine and aconine, worked out by Dunstan and Cash, largely as the result of investigations made in this building, in which the differences in physiological effect have been correlated with the successive introduction of hydrogen for an acetyl and a benzoyl group, associated with particular oxygen atoms in the molecule.

THE PRODUCTION OF SYNTHETIC COMPOUNDS.

The synthesis of alkaloids being impracticable, the attention of chemists and pharmacologists has been concentrated on the study of pure synthetic products with the view of applying what was known about the alkaloids to the preparation of substitutes. In this way a large mass of material has been accumulated dealing with the specific physiological effect of various radicals. If we except chloral hydrate, introduced into medicine as the result of Liebreich's investigations, perhaps the earliest of these synthetic remedies, dating back to 1882 or 1883, were the antipyretics kairine, thalline, and others, derived from hydroxyquinoline—in the production of which may be traced the influence of M'Kendrick and Dewar's work—and among the latest are to be found anthraquinone derivatives, of which purgatin may be taken as typical. There is a fascination about this work which is not lessened by the puzzling nature of some of the results. The substance administered cannot in many cases be the substance that enters into reaction in the system, otherwise, to take a case, sulphonal and "reversed" sulphonal—in which the all important ethyl groups and non-essential methyl groups have changed places—would not have the same hypnotic effect. Nevertheless, it is now possible to speak with some degree of certainty of the physiological action of radicals like hydroxyl, amidogen, carboxyl or ethyl, and in some instances to build up substances such as sulphonal and trional, on the one hand, or to introduce

radicals into alkaloids—as, for example, in the conversion of morphine into codeine or heroine—on the other, in order that a given effect may be produced, enhanced or weakened.

Thus it comes about that side by side with alkaloids we find pure chemical substances, capable of being administered in exact doses and in a pleasant form, are being more extensively used every day, and it seems only reasonable to suppose that this practice will grow at the expense of the older, and that each succeeding Pharmacopœia will witness the elimination of more and more galenical preparations of uncertain strength, and their replacement by substances of exact chemical composition and well-established therapeutic action.

THE IMPORTANCE OF CHEMICAL TRAINING.

What, it may be asked, is the bearing of this on the work of the School of Pharmacy—on the training of the pharmacist, in other words. It seems to me that the connection is, or should be, a very close one. The medical practitioner and the pharmacist are the men to whom is committed the duty of providing the remedies required in combating illness, and it is surely of the first importance that both should have a sufficient knowledge of chemistry and pharmacology to follow the trend of modern research in the directions I have indicated. Indeed, the necessity for this in the case of the pharmacist is recognised in the Journal of the Society by the publication at frequent intervals of notes on new remedies in the weekly “Review of Current Work” in pharmacy and the allied sciences.

It is difficult to predict the place that chemistry will occupy in the medical curriculum a few years hence, as a result of the competition with the other subjects of which a knowledge is required before a student is qualified to practise. In the University of London a strong effort has been made of late—with what success I do not know—to relegate it to the period of preliminary medical studies, and to assign to it an altogether subordinate place in the training of a doctor. The study of *materia medica*, too, does not seem to be viewed with much greater favour. Such a policy is surely distinctly retrograde, for the proposal to substitute physiological chemistry for

organic chemistry in the intermediate examination does not meet the case—physiological chemistry, that is, the application of chemistry to the problems of physiology, can only be taught adequately on the basis of a sound knowledge of chemistry itself. If chemistry is to be crowded out of intermediate medical studies in this way, the pharmacist—supposing he takes advantage of the opportunity—may eventually not only be charged with the duty of providing drugs of known purity, but also be consulted about their properties.

THE STATUS OF THE PHARMACIST.

The question of the status of the pharmacist is a perennial subject of controversy—it was being discussed during my apprenticeship, and it is clearly a burning question now. Pharmacy, of course, is in the singular position of being at once both a profession and a trade, and whatever may be the case with regard to the latter aspect, there can be no doubt that the estimation in which it is held as a profession depends on the training its members receive. I have always thought it a misfortune that if two examinations be necessary the lower should be the qualifying one; but putting that aside, pharmacy can hardly expect to receive adequate recognition until a compulsory curriculum is enjoined for the qualifying examination. I gather from a recent number of the *Pharmaceutical Journal* that some of the newer Universities are giving facilities for training in pharmacy, and this is a hopeful sign, for no surer way of raising the status of the pharmacist could be found than for his scientific training to be gained in this manner.

The association of this School with the reconstituted University of London cannot, however, be said to be very close—the three professors are recognised teachers of the University, but that is all. Pharmacy is not yet recognised as a branch of applied chemistry by the authorities at South Kensington to the extent of including this School among the schools of the University, although a strong case could be made out in favour of its being placed on the footing that it occupies in this respect in German universities.

In this connection it cannot be too widely known that the Council has made provision for research both in chemistry and

pharmacy by equipping special laboratories for the purpose, and that by the munificence of the Salters' Company and of the donors of the Redwood, Burroughs, and Northway Butt scholarships, means have been provided to enable students to carry on research after they have completed the school curriculum. Thus it is that, although preparation for the Minor and Major examinations must be the main work carried on here, no student of the School can be ignorant of the fact that creation of new knowledge is regarded by the Council as one of the aims which a pharmacist should ever keep in mind. It must be with much satisfaction that those who have fostered the prosecution of research in this School have seen their far-sighted policy justified by the steady volume of original work—much of it of first-rate importance—which has issued from these laboratories since their establishment in 1888.

CONCLUSION.

I come now to the most pleasant part of the duty assigned to me by the Council—that of congratulating the prize-winners and those who were successful students in the past session. Some of you are leaving the School; but, although this is the case, I hope you will try to find some opportunity of carrying on your scientific studies. In every pharmacist's experience difficulties must arise and unexpected results be obtained, and the successful solution or explanation of these will bring in its train a sense of satisfaction which will more than compensate for the time and trouble involved, even if the results do not achieve the dignity of publication in the Journal. You cannot, perhaps, expect to have Scheele's good fortune and make discoveries such as those of oxygen or prussic acid, but I hope you will at least try to follow this great pharmacist's example of finding some time for science amid the cares of business, and of adding your contributions to the stock of knowledge.

It only remains for me to welcome those who have entered the School to-day for the first time. In doing so let me say this: The School to which you now belong is one that has been the nursery of many men who have become famous in pharmacy, chemistry, and medicine. I urge you to do all that lies in your

power to maintain its traditions and to add to its fame. You come to it with the varied practical experience gained as pupils or apprentices, and it should need no words of mine to impress on you the importance of using the next year or two years wisely and well. The opportunity of a year's study may never recur, and if you are to make the most of your time serious work must begin from to-day. Everyone knows how great the temptation is to take things easily at first, in the expectation of being able to make up arrears later on; but, believe me, no greater mistake can be made. Steady, persistent work is the only sure road to success, and if it be made the rule of your student life you will at least have deserved that full measure of success which I hope awaits you here and in the larger world outside.

